Sept 1, 1999

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

NOVARTIS

Aug. 31, 1999

Dockets Management Branch **(HFA-305)**
Food and Drug Administration
5630 **Fishers Lane,** Room 1061
Rockville, MD 20852

S u b j e Response to Draft Guidance for Industry on Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products; Chemistry, Manufacturing and Controls Documentation, (Federal Register, June 2, 1999, Docket 99D-1454)

To Whom It May Concern:

Novartis Pharmaceuticals Corporation has reviewed the above-referenced draft guidance. Specific comments, identified by line number, are provided in tabular form in the enclosure.

Novartis welcomes the creation of a guidance on nasal spray delivery systems and feels that much time and research has been done on this draft. However, Novartis believes that this guidance asks for an extensive amount of information that is either too restrictive, GMP-related, or not necessary for these products. Additionally, Novartis suggests that inhaled products be addressed in one guidance and those that are not inhaled be addressed in this guidance, since the requirements for inhaled products are clearly different.

Thank you for the opportunity to comment. If you have any questions, please contact Dr. Mathias Hukkelhoven at (973) 781-6035 or Sheryl LeRoy at (973) 781-2735.

Sincerely,

M Hukkelhoven

Dr. **Mathias Hukkelhoven**
Vice President, Head US DRA
US Drug Regulatory Affairs

99D-1454

C17

Enclosures: Comments provided in duplicate

Novartis' Comments on the Draft Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products

General Remarks

1. As with the DRAFT FDA Guidance for Metered-dose Inhalation and Dry Powder Inhalation products, this new draft guidance provides a complete set of requirements for drug products in general as well as those requirements specific to these dosage forms. It is, however, more consolidated than the former draft.
2. There is a clear and logical distinction between the requirements for the different routes of administration, namely nasal and lung; for example in sterility requirements and in plume geometry. Therefore, we suggest that all inhalation products be covered in a separate guidance, since the degree of concern related to the routes of inhalation and nasal application are quite different.
3. There are numerous new criteria and very strict requirements listed within this guidance. Some of these requirements are excessive, especially with regard to nasal spray solutions and the demand for sterility of inhalation liquids.
4. In reference to the Stability, Container Closure and Labelling requirements noted in this guidance, a direct reference to the other appropriate approved guidances is recommended. The only additional information included in this guidance should be information which is specific to the dosage forms, described herein.
5. The requirements for post-NDA approval changes are not clear. We look forward to a guidance on post-approval changes for nasal delivery drug products.
6. We are concerned that the requirements listed in this guidance will be enforced for some older NDAs when sponsors submit submissions for simple changes. This has occurred in the past and is of great concern, since applying new requirements to hold up approvals for improvements to existing products has a great impact on drug supplies for patients.

Lines	Comments
3-15	We propose that all inhalation products be covered in one guidance, i.e. the DPI/MDPI can be added with (non pressurized) inhalation solutions and suspensions.
37	Airless systems which are pressurized i.e. by inert gas, but not by a propellant, should be included in this guidance.
55	Please change "actuator and its orifice" to "pump, any connecting parts and its orifice"
68	Inhalation solutions/suspensions/sprays should not be required to be sterile.
74	These drug products are not always designed for unit dosing. Quite a few preparations are made as multi-dose nebulizer solutions.
125	Drug product formulation: this should specify whether components include the container and packaging as defined previously. It is unclear.

209-275	It seems inappropriate to make the requirements for excipient characterization more stringent for inhaled drugs than for injected dosage forms, especially if a more complete characterization of the excipient would have no impact on the dose delivery (functionality of the system).
218-226	Requiring identification of suppliers for excipients used in suspension formulations, and data in support of changing these suppliers, is too stringent (especially for compendia1 materials). In-house raw material selection criteria are used to assure equivalent quality requirements. The sponsor should be responsible for assessing a new supplier's ability to provide material that meets the same acceptance criteria, not the Agency.
245-256	Supplier validation is an internal activity which should be performed as per GMP's or maybe through a PAI inspection, rather than within the NDA.
258	Toxicological evaluation of a compendial excipient used in dosage forms administered via the inhalation route is excessive.
279	Building number should not be required as part of the manufacturing address. This is inconsistent with other guidelines where this is not specified (only the street address). This item can be covered in a PAI and does not need to be in the application.
284-285	As previously stated (lines 218-226) the excipient manufacturer need not be identified (name and address), when an excipient meets the requirements of the USP/NF.
292-293	Sterility of inhalation solutions, suspensions and spray drug products should not be required and is not necessary. For suspensions this requirement is almost impossible to achieve. Micronization of drug substance via jet milling is not possible under sterile conditions, hence the only alternative would be y-irradiation of the micronized drug substance, which will be very limited.
308	Clarification of the level of detail needed for the packaging process description is needed. Also, please note that this is in reference to primary packaging and not secondary packaging.
325-328	If secondary packaging of a protective nature for the drug product (such as an overwrap) is performed by a contract packager, the information pertaining to the integrity of the package should be provided by the contract packager's drug master file (if available), or should be assessed by the district office during the pre-approval inspection.
373	Enantiomeric specific identification testing should not be needed for drug product release testing. The correctness of the specified enantiomer should be demonstrated in the drug substance. Enantiomeric testing should be performed on a process qualification basis and not as a release test.
377-386	Drug content assay should be based on the concentration of the solution (or suspension) and not on the amount in the entire container. The amount in the container is accounted for in the Net Content test (line 568). The concentration of the solution is the critical factor in delivering the correct dose.
404-413	Pump delivery could be an acceptance criterion for the pump, but it should not be a release specification for the product. This would be controlled by the Spray Content Uniformity Test.
412-413	The proposed requirements cannot be met by all pumps on the market. Additionally, the influence of some bubbles due to handling and a slight decrease of performance during shelf life should be taken into account. The "individual +/- 15% and mean +/-10 % of the target weight," are too tight. These limits should be changed to individual +/-20% and average +/-15 %.
415-474	Spray content uniformity and spray content uniformity through container life tests should not be required for solutions. For suspensions, these tests may be relevant, but the requirements should be less restrictive.

415-447	The SCU test requires collecting the discharged spray and analyzing it for content. This can be a major problem, especially with nasal sprays delivered vertically. If any of the spray is lost during collection (or a drop falls out of the collection device), a significant error is introduced. For nasal spray solutions, measuring the weight change and using the assay value should give good values for the amount delivered without the possibility for major errors.
449	Please give the rationale for including a spray content uniformity test throughout the shelf life of the drug product.
449-474	If the 10 determinations include the first delivery that is measured in the previous test (SCU), then can we use the data from that test as part of this one? Otherwise, we are duplicating testing.
476-480	Spray pattern should be regarded as sufficient. "Plume geometry" should be deleted.
482-488	These lines should be modified or deleted. Since spray pattern is affected by nozzle dimensions, pump and metering chamber as well as formulation, and these are all defined by dimensional and physical specifications, there is no need for spray pattern testing as a routine test. This test is a very qualitative, operator-dependent test and contributes very little to the quality and efficacy of a nasal spray product.
497	The example for longest and shortest axis of "1 .00 to 1.20" is too restrictive. Please delete the example. The possibility of evaluation of the spray angle (e.g. maximum and minimum spray angle to cover size and shape) should be added.
497-500	Delete this sentence on spray pattern determination. Different distances may not be suitable, since the distance with optimum detection should be evaluated; drug specific methods are not necessary. Add the following: "It might be useful to compare water, placebo and drug product results to allow routine control of pumps with placebo only."
500-502	For spray pattern testing, the measurements can be very subjective depending upon where the analyst thinks the edge of the pattern is. Using a more sensitive detection procedure, as suggested, means that fainter material will be seen, possibly making the determination of the edge harder.
507	Please define cut-off values more clearly, i.e. ranges of sizes.
512	Calculation algorithms are complex and not easily available. Calculation algorithms should be replaced by the type of theory, and possible use of correction principles (i.e. for optical density).
552-553	Allowing products to meet the acceptance criteria in USP <1111>, Microbiological Attributes for Nonsterile products is a contradiction to the definition given in line 81, which says that Inhalation solutions should be Sterile Products.
585-586	Identification, monitoring and quantification of the leached components during development should be deleted. Identification and/or toxicological evaluation might be required for substances of more than 0.1% peak area, as compared to the drug substance.
580-591	This entire paragraph should be revised accordingly to the comment above. For nasal sprays, the total weight of extractables from the critical components should be sufficient.
628-631	Sterility requirements should be deleted.
639-640	Foreign particles < 10 micrometer: it is difficult to discriminate between foreign and non-foreign panicles in this range.

703-704	The provision to evaluate and define the shape of the complete individual spray plume over time is not necessary. Plume geometry should only be used as an exemption where particle/droplet size distribution and spray pattern are not sufficient tests to assure consistent dosing to the patients.
760	The recommended recovery between 85% and 115% seems to be very restrictive. It should be noted that a broader range would be acceptable.
782	Please see the comment on line 512 addressing calculation algorithms.
797	Please change "container closure" to "dose delivery system".
842	Information on sampling plans for container/closures is a GMP issue and should not be included in the guidance.
845-846	Please replace the reference to the 1987 Packaging Guidance with a reference to the May 1999 FDA Guidance as this has now been issued. Delete footnote 7.
848-868	Please note that this information could be provided in the pump manufacturer's drug master file.
860	Please see the comment on lines 585-586, addressing toxicological evaluation of extractables.
864-865	The types of pump components to be profiled should be specified. Please note that either critical or primary components should be profiled for extractables.
889-922	Control extraction studies: If industry were to completely comply with the stated requirements for the control extraction studies, it would make the use of the dose delivery devices described in this guidance prohibitive. The Agency should provide a rationale noting why such stringent testing should be performed on the subject materials. It does not seem justifiable to require the amount of supportive data that is requested here. It seems that there is a requirement to use multiple solvents to evaluate possible extractables. A toxicological evaluation of all the possible extractables, even if they are never in the product and would not be extracted using the formulation, is extreme. Routine extraction should only be done with the formulation or placebo. There is no need to use solvents that will never be in contact with the components during routine manufacture and use. Information on extraction studies and toxicology of the extractables may be performed by the supplier and given in their drug master file. The guideline should indicate this. This may also be the case for the composition of the pump parts.
926-937	Routine extraction does not need to be performed on every container, closure, and pump component. Although extractable tests are valuable in determining the potential effect on the formulation, and thus to the patient, once extractable profiles are established and the quality from the source is assured it is not be necessary to routinely test every batch of component. Extractions can be done when changes to the packaging components are made, to ensure a similar profile. Additionally, the use of water and one organic solvent should be sufficient.
935	For nasal sprays the total weight of extractables from the critical components should be sufficient.
947	Specifications for individual pump components are the responsibility of the pump manufacturer and belong in their drug master file.
981-1006	Some of the information such as the statistical approach, content and format of stability data, commitments and especially expiration dating period don't belong in the stability protocol. The source of the containers and excipients should not be included if an in-house program for establishing comparability exists. Many of these comments were previously provided during review of the draft stability guideline. Therefore, the current draft guideline should refer to the stability guideline for specifics.

1025	For consistency the guidance should refer to the intermediate test condition as the ICH 'fallback" condition.
1027	The Office of Generic Drugs only requires three months accelerated stability data instead of the ICH required six months of accelerated data. This is inconsistent.
1044-1046	Including secondary packaging components in stability studies is only appropriate for semi-permeable primary containers.
1095-1097	The source of excipients need not be specified in stability documentation.
1104-1107	Sampling plans are a GMP consideration and should not be addressed in this guidance.
1119-1127	The requirement of three different batches of containers and closures is excessive. Additionally, this is treated in the stability guidance. A reference to this guidance is appropriate here.
1134	See comments on specifying excipient suppliers, on lines 218-226
1141 to 1148	These requirements are linked to site-specific stability issues still under discussion with the FDA. We continue to have the concerns already presented to the FDA on that topic, especially on the requirements iterated here; for multiple facilities and sources, bracketing and matrixing is actively discouraged. These concerns should continue to be the subject of the stability guidance.
1174-1175	Dose volume should be sufficient to evaluate various orientations. SCU is not necessary.
1195-1210	Requirements for temperature cycling studies should be different for nasal sprays and inhalation products.
1200-1204	The temperature cycling program that is proposed, 3 or 4 cycles, 6 hours each, per day would mean that an analyst would need to be on stand-by around the clock for 4 weeks. This is not justified. Longer cycles should be adequate to evaluate the effects of temperature cycling.
1206	SCU, SCU through container life, and sterility should not be requirements for the cycling studies. Dose volume is an adequate measure for this study.
1227	Clarification of the type of studies expected to establish performance characteristics would be useful.
1240	Replace "SCU and particle/droplet size distribution" by pump delivery (delivery volume) for all solutions.
1264-1265	Replace "delivered drug substance and droplet size distribution" by pump delivery (delivery volume).
1278-1287	See comments on plume geometry (lines 703-704)
1321	Determination of the stability of a product after unpacking it is important for such pre-packed products. Extrapolation of the data achieved on unpacked product at the beginning of the stability testing period, however, should be allowed to determine the potential stability of product unpacked toward the end of its expiry date. For first submissions product in its intended market formulation is often not 'old' enough to evaluate this.
1335-1557	Labelling should be the subject of a more general labelling guidance. Alternatively, include only that information which is dosage form specific.

PRO 6.0.1818 S6400

NOVARTIS PHARMACEUTICAL CORPOR
(973)781-8769
INTERNAL DISTRIBUTION
101 - MAILROOM - 083199
59 ROUTE 10 EAST
EAST HANOVER NJ 07936-3723

1 LBS

SHIP TO: FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION
HFA-305
DOCKETS MANAGEMENT BRANCH
5630 FISHERS LANE
ROCKVILLE MD 20852

MD 2070-10

UPS NEXT DAY AIR

TRACKING #: 1Z 275 8W6 01 4095 5347

ACCT. CODE:802208
COST UNIT:8830

Call 1-800-PICK-UPS (1-800-742-5877) or visit our Web site at www.ups.com

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

EXTREMELY URGENT

UPS Next Day Air®

United Parcel Service, Louisville, KY